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DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/891,865	BESTETTI ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31 and 33-66* is/are pending in the application.

4a) Of the above claim(s) *49-57 and 60* is/are withdrawn from consideration.

5)☒ Claim(s) *43* is/are allowed.

6)☒ Claim(s) *31,33-42,44-48,58,59 and 61-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 31 and 33-66 are pending in the application.

[2] Applicants' amendment to the claims, filed March 31, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] It is noted that applicants state, "[a]fter entry of the present amendment, claims 31 and 33-64 are pending" (page 12, lines 2-3 of the response). However, this statement is incorrect. As claims 65-66 have been added in the instant amendment, claims 31 and 33-66 are pending.

[4] Applicants' amendment to the specification, filed March 11, 2004, is acknowledged.

[5] Receipt of a computer readable form (CRF) of the sequence listing, a paper copy thereof, a statement that this paper copy of the sequence listing includes no new matter, and a statement of the sameness of the CRF and the paper copy of the sequence, filed March 11, 2004, is acknowledged.

[6] Receipt of an information disclosure statement, filed March 11, 2003, is acknowledged.

[7] Receipt of a claim to foreign priority under 35 USC § 119(a)-(d), filed April 06, 2004, is acknowledged.

[8] Claims 49-57 and 60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[9] Claims 31, 33-48, and 58-59, and 61-66 are being examined on the merits.

[10] Applicants' arguments filed on March 31, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[11] The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

Priority

[12] As stated in a previous Office action, the foreign priority document (MI 98 A 002792) has not been received by the Office and applicant has not been granted the benefit of foreign priority as the conditions of 35 USC § 119(a)-(d), particularly 35 USC § 119(b), have not been satisfied. Applicants' statement that this document "will follow" is acknowledged.

[13] Applicants' claim to foreign priority under 35 USC § 119(a)-(d) to Itay Application 1304500, filed March 19, 2001, is acknowledged. Receipt of the foreign priority document is acknowledged.

Specification/Informalities

[14] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Vectors, Host Cells, and Methods for Production of Uridine Phosphorylase

and Purine Nucleoside Phosphorylase". It is noted that applicants have amended the title, which states (in relevant part) "Vectors, Host Cells, and methods for Production of... ...Purine Nucleotide Phosphorylase" (underline added for emphasis). It is noted that the claims are drawn to vectors, host cells, and methods for production of purine nucleoside phosphorylase (underline added for emphasis; see, e.g., claim 31). Appropriate correction is required.

Claim Objections

[15] In view of the amendment to the claims, the objections to claims 39-40 and 43 as set forth in items [12] and [13] of the Office action mailed December 11, 2003 are withdrawn.

[16] Claim 31 is objected to in the recitation of "/or." It is suggested that applicants replace "/or" with, for example, "or."

[17] Claim 48 is grammatically incorrect in the recitation of "[m]ethod of producing." It is suggested that the claim be amended to recite, for example, "[a] method of producing."

[18] Claim 61 is objected to as reciting "[a] prokaryotic host cell according to claim 44." It is noted that claim 44 is drawn to a plurality of "[p]rokaryotic host cells." It is suggested that applicants reconcile the use of the singular/plural form of cell(s) in the claims.

[19] Claims 63-64 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 61-62, respectively. When two claims in an application are duplicates or else

are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). It is noted that, while claims 63-64 are limited to "[a] transformed prokaryotic host cell," absent evidence to the contrary, one of skill in the art recognizes that a host cell containing a plasmid expression vector has necessarily been transformed with that vector. Thus, claims 63-64 are substantially identical to claims 61-62.

Claim Rejections - 35 USC § 112, Second Paragraph

[20] In view of the amendment to the claims, the rejection to claims 33, 35-38, 42, and 46-48 under 35 USC, second paragraph, as set forth in item [15] of the Office action mailed December 11, 2003 is withdrawn.

[21] Claim 61-62 and 65-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

[a] Claim 61 (claim 62 dependent therefrom) recites the limitation "the prokaryotic host cell not containing the plasmid." There is insufficient antecedent basis for this limitation in the claim. In order to perfect antecedent basis, it is suggested that applicants replace "the prokaryotic host cell not containing the plasmid" with, for example, "a prokaryotic host cell not containing the plasmid."

[b] Claims 65-66 are confusing as the claims are drawn to "[a] plasmid vector according to claim 63," however, claim 63 is drawn to "[a] transformed prokaryotic host cell." It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[22] The written description rejection of claim(s) 31, 33-42, 44-48, 58-59, and 61-66 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [16] of the Office action mailed December 11, 2003 and for the reasons stated below.

[23] RESPONSE TO ARGUMENTS: Applicants argue the claims comply with the written description requirement as the claims are drawn to plasmids comprising sequences that were well-known in the art at the time of the invention and are not drawn to a novel genus of genes encoding polypeptides having UDP or PNP activity. Applicants argue the udp and deoD gene sequences of E. coli as recited in claims 36 and 38 were known and publicly available at the time of the invention, citing Database EMBL Accession Numbers X15689 and M60917 as evidence thereof. Applicants cite the references of Takehara et al. and Hershfield et al. (both cited in the IDS filed June 25, 2001) as providing additional examples of udp and deoD gene sequences. Applicants argue that because udp and deoD gene sequences from mesophilic bacteria were known in the art at the time of the invention, a skilled artisan would recognize that applicants were in possession of the claimed invention, citing MPEP 2163, which states (in summary) that information that is well known need not be described in the

specification. Applicants note that claim 34 limits the mesophilic bacteria to E. coli and argue that since this organism is well-characterized, a skilled artisan can easily identify, characterize, and use a udp and/or deoD gene sequence(s) from this organism. Applicants' argument is not found persuasive.

Regarding claims 31, 33-35, 37, 39-42, 44-48, and 58-66, the examiner acknowledges that the claims are not drawn to the udp and deoD gene sequences themselves, however, these sequences are an essential element of the claimed invention and must have adequate written description in accordance with MPEP 2163, which states:

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art."

While it is acknowledged that Escherichia coli udp and deoD gene sequences were known in the art at the time of the invention, the claims are not so limited to these sequences. Instead, the claims encompass any udp and deoD gene sequences, including mutants and variants of those sequences that ARE known. At least for this reason, the genus of mesophilic bacterial gene sequences coding for polypeptides having uridine phosphorylase activity and/or purine nucleoside phosphorylase activity have not been adequately described in the specification. Moreover, the genus has been described only by functional features. As stated in a previous Office action, the CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that:

> "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One

> skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus."

Similarly with the claimed genus of genes, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus, which distinguish the species encompassed by the genus from others such that one can visualize or recognize the identity of the members of the genus.

Regarding claims 36 and 38, while the sequence of the udp or deoD gene is limited to a specific nucleic acid sequence, it is noted that the sequence of the other gene is not limited to a specific sequence, and thus, because the sequence of the other gene is not fully described at least for those reasons stated above, these claims also fail to meet the written description requirements.

Given the lack of description, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[24] The scope of enablement rejection of claim(s) 31, 33-42, 44-48, 58-59, and 61-66 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [17] of the Office action mailed December 11, 2003 and for the reasons stated below.

[25] RESPONSE TO ARGUMENTS: Applicants argue: 1) the sources of the respective sequences are limited to mesophilic bacteria; 2) sequences of udp and deoD were known in the art at the time of the invention and only routine experimentation is required to retrieve other udp or deoD sequences; 3) the instant situation is analogous to In re Wands in that routine screening can be used to isolate udp and deoD genes; 4)

claim 34 limits the mesophilic bacteria to E. coli, claims 35 and 37 limit the sequences to a udp or deoD gene of E. coli, and claims 36 and 38 limit the udp or deoD sequence to a specific nucleic acid sequence; and 5) that simple and well-established techniques can be used to "avoid or reduce" the unpredictability of modifying an encoding nucleic acid sequence, citing the reference of Hershfield et al. (supra). Applicants' argument is not found persuasive.

The specification, while being enabling for an expression vector comprising the nucleic acid of nucleotides 243-1021 of SEQ ID NO:1 encoding E. coli uridine phosphorylase or the uridine phosphorylase mutants as described by Hershfield et al. (supra) and the nucleic acid of nucleotides 231-960 of SEQ ID NO:3 encoding E. coli purine nucleoside phosphorylase OR an expression vector comprising Klebsiella sp. LF 1202 udp and deoD genes as described by Takehara et al. (supra), does not reasonably provide enablement for the full scope of the claims.

There is no dispute that the sequences of the genes encoding polypeptides having uridine phosphorylase activity and purine nucleoside phosphorylase activity of the claimed plasmids are limited to those of a mesophilic bacterium. While working examples of E. coli and Klebsiella sp. LF 1202 udp and deoD gene sequences were known at the time of the invention (as cited by applicants in the response to the written description rejection), claims 31, 33-35, 37, 39-42, 44-48, 58-59, and 61-66 are not so limited to these working examples, and instead broadly encompass any genes coding for polypeptides having uridine phosphorylase activity and purine nucleoside phosphorylase activity from any mesophilic bacterium (claims 31, 33, 39-42, 44-48, 58-

59, and 61-66), any genes coding for polypeptides having uridine phosphorylase activity and purine nucleoside phosphorylase activity from E. coli (claim 34), or any sequence of a udp or deoD gene from E. coli (claims 35 and 37), including mutants and variants thereof that have UDP or PNP. The specification fails to provide guidance regarding the relationship of the nucleotide sequence of the working examples to other mesophilic bacterial genes coding for polypeptides having uridine phosphorylase activity and purine nucleoside phosphorylase activity, e.g., a region conserved among all species, such that these working examples can be used to isolate other mesophilic bacterial genes coding for polypeptides having uridine phosphorylase activity and purine nucleoside phosphorylase activity. Also, the specification fails to provide guidance regarding those modifications to the mesophilic bacterial genes coding for polypeptides having uridine phosphorylase activity and purine nucleoside phosphorylase activity that can be made with an expectation of obtaining an encoded polypeptide having the desired activity. While Hershfield et al. (supra) may disclose representative mutants of wild-type E. coli deoD gene, the claims are not so limited to those mutants as taught by Hershfield et al. (supra) and, moreover, there is zero guidance provided in the specific and prior art regarding modification of an E. coli udp gene.

The examiner disagrees with applicants' assertion that the instant case is analogous to In re Wands. In Wands, the epitope for generating the claimed antibodies and methods of production thereof were known, thus, one would have a reasonable expectation, based on the teachings of the specification and the prior art, that the antibodies generated against that epitope would bind to that epitope and could be used

in the claimed method of immunoassay. In contrast to Wands, one of skill attempting to make the entire scope of claimed expression vectors, would not have the benefit of such a reasonable expectation. For example, in this case, there is no evidence that the known sequences of mesophilic bacterial genes encoding polypeptides having uridine phosphorylase activity and purine nucleoside phosphorylase activity can be used to identify the corresponding genes in other mesophilic bacteria based on known methods that require a high degree of homology, e.g., hybridization. Moreover, the specification fails to provide guidance for altering the sequences of these genes with an expectation of obtaining a nucleic acid that encodes polypeptides maintaining uridine phosphorylase activity and purine nucleoside phosphorylase activity. The effects of such alterations on the function of an encoded protein are highly unpredictable as evidenced by Branden et al. and Witkowski et al., the teachings of which are undisputed by applicants.

Regarding claims 36 and 38, while the sequence of the udp or deoD gene is limited to a specific nucleic acid sequence, it is noted that the sequence of the other gene is not limited to a specific sequence, and thus, because the sequence of the other gene is not so limited, the scope of these claims also fails to be fully enabled by the specification.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high degree of unpredictability as evidenced by the prior art, and the significant amount of experimentation required to make the claimed invention, undue experimentation would be necessary for a skilled artisan to make the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

[26] The rejection of claim(s) 31, 34-38, 40-42, 44-48, 58-59, and 61-66 under 35 U.S.C. 103(a) as being unpatentable over Krenitsky et al. in view of Walton et al., Hershfield et al., Bulow et al., and Novagen 1997 Catalog is maintained for the reasons of record as set forth in item [18] of the Office action mailed December 11, 2003 and for the reasons stated below.

[27] It is noted that applicants' arguments address both rejections under 35 USC 103(a). To the extent applicants' arguments address the instant rejection, applicants arguments are rebutted below.

[28] RESPONSE TO ARGUMENTS: Applicants argue that the primary reference of Krenitsky et al. teaches away for the claimed invention in that Krenitsky et al. teach that for a high product yield of imidizo(4,5-c)pyridine derivatives, crude enzyme preparations must be purified so that the enzymes are removed from other components present in the cell. Applicants argue this is in direct contrast to the claimed invention, where high yields of product can allegedly be achieved with the enzymes remaining in a cellular environment, citing claims 61 and 63. citing In re Mills, applicants argue that the Krenitsky et al. reference cannot be combined with the other references to arrive at an expression plasmid for use in a cellular system. Applicants' argument is not found persuasive.

It appears that applicants have misinterpreted the rejection, particularly the teachings of Krenitsky et al., and how these teachings apply to the instant rejection.

There is no dispute that Krenitsky et al. teach "crude enzyme preparations are less suitable than purified preparations" (column 4, lines 30-31) and "it is desirable to purify the crude enzyme preparations before addition to the reaction mixture" (column 4, lines 41-43). In agreement with the teachings of Krenitsky et al., the examiner rejected the claims, not for use of *host cells* expressing UDP and PNP (to practice the method of Krenitsky et al. for the production of imidizo(4,5-c)pyridine derivatives), but for the use of a *purified UDP/PNP fusion protein* to practice the method of Krenitsky et al. As stated in a previous Office action:

> "[I]t would have been obvious to one of ordinary skill in the art to combine the teachings of Krenitsky et al., Walton et al., Hershfield et al., Bulow et al., and Novagen 1997 Catalog to generate a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme fused directly or via a peptide linker by appropriately inserting nucleic acids encoding *E. coli* uridine phosphorylase and purine nucleoside phosphorylase into plasmid pET29c followed by transformation of competent *E. coli* followed by expression and purification of the encoded fusion enzyme for use in the method of Krenitsky et al." (underline added for emphasis; page 13, top of the Office action mailed December 11, 2003).

Thus, examiner has stated that one would express a UDP/PNP fusion protein, purify the protein, and use it in the method of Krenitsky et al. Nowhere does the examiner state that the method of Krenitsky et al. can be practiced using a host cell expressing UDP and PNP. Contrary to applicants' assertion, the teachings of Krenitsky et al. do not contradict the claimed invention. While applicants assert, "high yields of product can be achieved with the enzymes remaining in... ...a host cell" (page 21, first full paragraph), it is noted that applicants' arguments are not commensurate in scope with the claims as none of the elected claims are drawn to methods of producing a product in high yield using the expressed enzymes in a host cell. The claimed invention is drawn to a recombinant expression vector comprising a gene encoding a mesophilic bacterial

uridine phosphorylase enzyme and a gene encoding a mesophilic bacterial purine nucleoside phosphorylase, host cells comprising said expression vector, and methods for producing a fusion protein using said host cells. While non-elected method claims, e.g., claim 49, are drawn to the use of the claimed plasmid for catalyzing transglycosylation using a host cell comprising the claimed plasmid, the elected claims are not drawn to such methods. Therefore, contrary to applicants' assertion, Krenitsky et al. clearly do not teach away from the claimed invention and the combination of cited references would have rendered the claimed invention obvious at the time of the invention.

Applicants argue the combined references do not provide a reasonable expectation of success. In support of their argument, applicants cite a particular teaching of Krenitsky et al., which states (in summary) that the UDP and PNP enzymes of the thermophile B. stearothermophilus and the mesophile E. coli are effective for production of imidizo(4,5-c)pyridine derivatives. Applicants further cite JP-06-253854 (cited in the IDS filed June 25, 2001) as teaching that the expression of B. stearothermophilus UDP and PNP yielded only a 6-8 fold improvement compared to a non-transformed control. Applicants argue that since the Krenitsky patent teaches that thermophilic and mesophilic enzymes are both effective, and since JP-06-253854 shows that thermophilic enzymes are not particularly effective, the skilled artisan would not have had any reasonable expectation that a plasmid expression vector based on mesophilic enzymes would have been successful or even worthwhile to pursue prior to the present invention and that none of the other references cited by the examiner would

have given the skilled artisan a reasonable, or at least improved, expectation of success in obtaining a plasmid effective for conducting UDP and PNP reactions in a recombinant system since all of the remaining references are silent as to any PNP or UDP activity testing in recombinant systems. Applicants' argument is not found persuasive.

It is noted that, at least for claims other than claims 61-66, applicants' arguments are not commensurate in scope with the claims. Claims other than 61-66 do not recite a required level of expression of UDP and/or PNP. Regarding all rejected claims, it is noted that the reference of JP-06-253854 does not teach away from using an E. coli UDP/PNP fusion enzyme for practicing the invention of Krenitsky et al. as the method of Krenitsky et al. requires no particular level of expression of UDP and PNP enzymes, only that the enzymes can be obtained by purification. Furthermore, while JP-06-253854 may provide a comparison of UDP and PNP expression in B. stearothermophilus, Krenitsky et al. and JP-06-253854 are silent as to the level of UDP and PNP overexpression in E. coli. Although Krenitsky et al. state that UDP and PNP from B. stearothermophilus and E. coli are both "effective" for the production of imidizo(4,5-c)pyridine derivatives, this statement provides no indication that the recombinant production of the enzymes in B. stearothermophilus and E. coli would be equivalent. Furthermore, it is noted that the examiner has stated in the rejection that the genes encoding E. coli UDP and PNP would be inserted into plasmid pET29c, which the manufacture claims is "the most powerful system yet for the... expression of recombinant proteins in E. coli" (page 42 of Novagen 1997 Catalog). Thus, one would have a reasonable expectation of success that, by using the pET29c vector for

expression of genes encoding E. coli UDP and PNP, a high yield of expression would be obtained. In this regard, the Office does not have the facilities for examining and comparing applicants' UDP and/or PNP activity in the host cell of claims 61-66 with that of the prior art. Thus, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the level of UDP and PNP activity as expressed in an E. coli host using the pET29C vector does not possess the same material characteristics of the claimed host cell). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

[29] The rejection of claim(s) 31, 34-39, 41-42, 44-45, 47-48, and 61- under 35 U.S.C. 103(a) as being unpatentable over Krenitsky et al. in view of Walton et al., Hershfield et al., Bulow et al., and Sambrook et al. is maintained for the reasons of record as set forth in item [19] of the Office action mailed December 11, 2003 and for the reasons stated below.

[30] RESPONSE TO ARGUMENTS: Applicants arguments and the examiner's responses thereto as stated above are reiterated herein. For the reasons set forth above, the cited references would have rendered the claimed invention obvious to one of ordinary skill in the art at the time of the invention.

[31] Claim(s) 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Krenitsky et al. in view of Walton et al., Hershfield et al., Bulow et al., and Sambrook et al. as applied to claims 31, 34-38, 41-42, 44-45, and 47-48 above, and further in view of

Noguchi et al. (JP 6-253854; cited in the IDS filed March 11, 2004). Claim 33 limits the expression vector of claim 31 to recited elements being inserted into a pUC18 plasmid.

Krenitsky et al. teach a method for the preparation of imidizo(4,5-c)pyridine derivatives using an aqueous suspension comprising *E. coli* purine nucleoside phosphorylase and uridine phosphorylase (see Examples 1 and 2). Krenitsky et al. teach that *E. coli* B was found to be an excellent source of the enzymes for practicing their method (column 4, lines 20-24) and that the enzymes are preferably purified (column 4, lines 41-43). Krenitsky et al. do not teach an expression vector comprising genes encoding mesophilic bacterial uridine phosphorylase and purine nucleoside phosphorylase, a gene encoding tetracycline and/or kanamycin resistance, and a transcription control sequence inserted into a pUC18 plasmid.

Walton et al. teach the nucleic acid sequence of the *E. coli udp* gene encoding uridine phosphorylase.

Hershfield et al. teach the nucleic acid sequence of the *E. coli deoD* gene encoding purine nucleoside phosphorylase (page 7186).

Bulow et al. teach recombinantly fusing enzyme-encoding nucleic acids to produce a bifunctional fusion enzyme with the component enzymes attached via a peptide linker (page 230, left column, top) and a method for preparation thereof (page 227). Bulow et al. teach numerous advantages of fusion enzymes including proximity effects (page 226, right column, bottom to page 227, left column, top and page 231, right column, top) and ease of purification requiring the purification of only a single fusion enzyme instead of two separate enzymes (page 231, left column, middle). Bulow

et al. acknowledge that the preparation and use of such fusion enzymes is well known in the art by disclosing "[o]ver the years, a variety of artificial bifunctional enzymes have been prepared by gene fusion *in vitro*" (page 227, right column, bottom).

Sambrook et al. teach selectable markers encoded by a plasmid are used to select for those clones comprising the plasmid (page 1.5). Sambrook et al. teach tetracycline is one of the most commonly used selectable markers (page 1.5) and further disclose, "[v]irtually all plasmid vectors in common use carry one or more of the antibiotic resistance genes described above" including tetracycline (page 1.6).

Noguchi et al. suggest the use of a pUC18 vector (see page 19, line 7) comprising a promoter (page 18, lines 13-22) for high-level expression of a recombinant protein in a bacterial host cell (page 20, top). Noguchi et al. further teach the use of tetracycline as a selection agent (page 21, line 7) in the expression of a recombinant protein.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Krenitsky et al., Walton et al., Hershfield et al., Bulow et al., Sambrook et al., and Noguchi et al. to generate a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme fused directly or via a peptide linker by appropriately inserting nucleic acids encoding *E. coli* uridine phosphorylase and purine nucleoside phosphorylase into a pUC18 plasmid comprising a promoter and a tetracycline resistance gene followed by transformation of competent *E. coli* and expression and purification of the encoded fusion enzyme for use in the method of Krenitsky et al. One would have been motivated to use a pUC18 vector comprising a

promoter and a tetracycline resistance gene for the expression of a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme because of the teachings of Noguchi et al., who specifically suggests using a pUC18 vector comprising a promoter and using tetracycline as a selection agent and the teachings of Sambrook et al., who teach the widespread use of a tetracycline resistance gene as a selectable marker (as described above). One would have a reasonable expectation of success for generating a uridine phosphorylase-purine nucleoside phosphorylase fusion enzyme fused via a peptide linker by appropriately inserting nucleic acids encoding *E. coli* uridine phosphorylase and purine nucleoside phosphorylase into a pUC18 plasmid comprising a promoter and a tetracycline resistance gene followed by transformation of competent *E. coli* and expression and purification of the encoded fusion enzyme for use in the method of Krenitsky et al. because of the results of Krenitsky et al., Walton et al., Hershfield et al., Bulow et al., Sambrook et al., and Noguchi et al. Therefore, claim 33, drawn to the expression vector as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[32] Status of the claims:

- Claims 31 and 33-66 are pending.
- Claims 49-57 and 60 are withdrawn from consideration.
- Claims 31, 33-42, 44-48, 58-59, and 61-66 are rejected.
- Claim 43 appears to be in a condition for allowance.

Applicant's amendment and submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on March 11, 2004 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

06-24-04